III. "Preliminary Account of an Inquiry into the Functions of the Visceral Nerves, with special reference to the so-called 'Inhibitory System.'" By JOSEPH LISTER, Esq., F.R.C.S. Eng. & Edin., Assistant Surgeon to the Royal Infirmary of Edinburgh; in a Letter to Dr. Sharpey, Sec.R.S. Received August 13, 1858. Communicated by Dr. SHARPEY.

MY DEAR SIR,—The fact that the irritation of visceral nerves sometimes causes arrest of the movements of organs supplied by them, as shown by Edward Weber's experiment of stopping the action of the heart by stimulating the vagus, and by Pflüger's more recent observation that the application of galvanism to the splanchnic nerves produces quiescence of the small intestines, appears to me to have an intimate bearing upon the question how inflammation is developed through the medium of the nervous system at a distance from an irritated part; and as the nature of the inflammatory process has lately engaged my especial attention, I have been led to make an experimental inquiry into this "inhibiting" agency, the true interpretation of which is, as you are aware, still *sub judice*. I now propose to state the principal results at which I have arrived, reserving further details for a more extended communication which I hope soon to offer to the Royal Society.

The view which has been advocated by Pflüger*, and I believe very generally accepted, viz. that there is a certain set of nerve-fibres, the so-called "inhibitory system of nerves" (Hemmungs Nervensystem), whose sole function is to arrest or diminish action, seemed to me from the first a very startling innovation in physiology; and you may possibly recollect my mentioning to you in conversation, when in London last Christmas, my suspicion that the phenomena in question were merely the effect of excessive action in nerves possessed of the functions usually attributed to them. On further reflection upon the subject, the consideration of the contraction produced in the arteries of the frog's foot by a very mild stimulus, as compared with the relaxation of the vessels caused by stronger irritants acting through the same nerves, confirmed my previous notions.

* Eduard Pflüger ueber das Hemmungs Nervensystem, 1857.

For I could hardly doubt that the cause of the quiescence of the heart or intestines on irritation of the vagus or splanchnic nerves was analogous to that of arterial dilatation in the web, and that, provided a sufficiently mild stimulus were applied to the so-called "inhibitory nerves," increased action of the viscera would occur, corresponding to the vascular constriction.

To test the truth of this hypothesis, I made several experiments between the 17th of June and the 14th of July of this year, with regard to the movements of the heart and intestines. The means used for stimulating the nerves and spinal cord were sometimes mechanical irritation, but more commonly galvanism, applied with a magnetic coil battery of a single pair of plates, the strength of which could be regulated in a rough way, with great facility, by the height at which the acid solution stood in the jar and the extent to which the rods of soft iron were inserted in the helix. The mildest action employed was such as was but just perceptible to the tip of the tongue, placed between the fine silver-wire extremities of the poles, when the rods were fully in the helix, but inappreciable after their complete withdrawal; the spring carrying the magnetic bar being made to vibrate by a touch with the finger: the greatest action of the battery, on the other hand, was so powerful as to elicit sparks when the poles were applied to the tissues.

My attention was first directed to the intestines, and it may be well to mention first all the results obtained with reference to them. The animals operated on were generally rabbits, they being very easily managed, and also favourable for the purpose on account of the large amount of movement which occurs in their intestines. Chloroform was generally not administered, on account of its depressing effect upon the action of the nervous centres.

In the first experiment, the ends of the poles having been fixed to the spinous processes of the ninth and twelfth dorsal vertebræ, according to Pflüger's original method, and the intestines allowed to protrude through a wound in the abdominal parietes, a series of interrupted currents were transmitted, a very small amount of acid being in the jar, and the rods fully in the helix. The effect was complete relaxation and quiescence of the small intestines, which had been previously in considerable movement, while the muscles of the limbs were thrown into spasmodic action; but on the discontinuance

of the galvanism the previous intestinal motion returned. The rods were then removed from the helix, and the battery, thus diminished, was applied on several occasions, with markedly increased action of the intestines in every instance during the first twenty-five minutes. In the next half hour the increase of action from the galvanism, though still distinct, was less strongly marked; and at the end of that period, the rods having been reintroduced, the inhibiting influence was also found to be much less complete than before, indicating that the parts of the nervous apparatus concerned were in a less active condition, no doubt in consequence of exhaustion. The arches of the tenth and eleventh dorsal vertebræ having been removed before the experiments with galvanism, I subsequently introduced a fine needle into the exposed part of the cord, with the effect of causing in repeated instances increased movements of the intestines, which were especially striking on account of the occurrence of peculiar local contractions not seen at other times. Further observations upon this animal tended to confirm those which have been mentioned, as did an experiment of the same kind performed the next day upon another rabbit.

I afterwards found that the best mode of proceeding was to remove the skin and one or two layers of muscles from a portion of the abdomen till the parietes were sufficiently thinned to permit the intestines to be distinctly seen through them; by this means the complication produced by exposure of the intestines to the atmosphere was avoided, and the most satisfactory results were obtained; the increase of the peristaltic movements during the transmission of extremely feeble shocks being strikingly apparent and constant on every occasion. During the experiment performed in this way I noticed several times that a violent struggle on the part of the rabbit, when the intestines were in pretty free movement, was followed by absolute and universal quiescence of those organs for several seconds; this appeared to me of great interest, as proving that the inhibitory influence is certainly sometimes exerted in the natural actions of the animal, and is not merely the result of artificial stimulation.

In the course of the above experiments several other observations were made. In the first place I verified the statement of Pflüger, that if, when the intestine is lying relaxed under the inhibiting

influence of galvanism applied to the spine, a particular part be irritated, local contraction occurs, but is not propagated to neighbouring parts. This fact is of fundamental importance, since it proves that the inhibitory influence does not operate directly upon the muscular tissue, but upon the nervous apparatus by which its contractions are, under ordinary circumstances, elicited.

Another point which seemed to require investigation was the well-known increase of peristaltic action which takes place after death, and which continues in spite of cutting off the mesentery close to the gut. Those who believe in a constantly restraining function of certain nerves during life might argue that the intestine has always a tendency to such active movements, but is kept in check by the "inhibitory nerves," and released from their control when they have lost their power after death. A different explanation, first suggested, I believe, by Bernard, is that the increased action of the intestines is the result of failure of the circulation in the part; and to this view I felt disposed to agree, in consequence of having noticed curious irregular contractions in the arteries of the frog's foot from a similar cause. In order to decide the question, I tied three adjoining arterial branches in the mesentery of a rabbit, thus depriving about 3 inches of the intestine of its circulation; the parts so affected being accurately defined by the extent of absence of pulsation in the minute vessels close to the gut. In about a minute and a half, vermicular movements commenced in this part; the rest of the intestines being at the time very quiet. Powerful interrupted galvanic currents were then transmitted through the posterior dorsal region of the spine, with the effect of causing perfect quiescence of the whole of the intestine, including the part whose arteries had been tied. After cessation of the galvanism the movements recurred in the portion devoid of circulation, while elsewhere they were almost entirely absent. This experiment was repeated on another occasion with similar results. In one of the cases I divided the mesentery close to the gut, after ligature of the vessels, but no change took place in the character of the movements which had been previously induced, indicating that the increased action in these cases had been of the same nature as that which results from death. The arrest of the movement on the application of galvanism proved that the delicate operation of ligature of the mesenteric vessels had been performed without

injury to the adjacent nervous branches; and it therefore followed that the movement in the parts supplied by those vessels was not due to any injury of the nerves, but simply to the arrest of circulation. It further appears from these experiments, that, in whatever way the cessation of the flow of blood through the vessels operates in increasing the peristaltic action, it does so through the medium of the nervous apparatus, and not by directly influencing the muscular tissue. For, in the latter case, the movement would have continued in spite of the inhibiting influence, which, as we have seen, has no effect upon muscular irritability.

The fact that the movements continue in a portion of gut deprived of its mesentery, proves that the nervous apparatus by which the muscular contractions are induced and coordinated in *post mortem* peristaltic action, is contained within the intestine.

The distinction between the coordinating power and muscular contractility was very strikingly shown in the further progress of one of these experiments. The peristaltic movements of the portion of gut supplied by the ligatured arteries ceased entirely about twenty minutes after the vessels were tied, and the surface of the gut became there perfectly smooth and relaxed, contrasting strongly with the wrinkled aspect of other parts. But muscular irritability had outlived the coordinating power, as was shown by energetic, purely local contraction taking place in a part pinched. Similar observations confirmatory of this point were afterwards made upon a rabbit which had died of hæmorrhage an hour before.

The mechanism by which the muscular contractions are regulated is, doubtless, the rich ganglionic structure lately demonstrated in the submucous tissue by Dr. Meissner of Bâle*. Professor Goodsir gave me the first information of this anatomical fact on my mentioning to him the foregoing physiological proofs of the existence within the intestines of a coordinating apparatus distinct from the muscular tissue. I have since verified Meissner's observations, and found abundant well-marked nerve-cells in the submucous tissue of the Ox, exactly corresponding with his descriptions.

But while muscular irritability outlives the coordinating power in the intestines, the latter lasts much longer than the inhibiting

* Henle and Pfeufer's Zeitschr. 2nd series, vol. viii.

property in the spinal system, for I find that Pflüger's experiment does not succeed in a dead animal, unless performed soon after death, although the intestines may continue to move for a long time.

In another experiment I divided with fine scissors, at a little distance from the intestine, all the visible branches of nerves in a portion of mesentery corresponding to an inch and three-quarters of the gut, leaving the vessels uninjured. No effect was produced on the peristaltic movements, which happened to be pretty active at the time, and continued the same at the seat of the operation as elsewhere. To ascertain whether the division of the nerves had been thoroughly effected, I now transmitted powerful galvanic currents through the spine, as in former experiments; when all movements ceased in the intestine, except in the small piece whose nerves had been cut, which continued in vigorous action as before. The persistence of the vermicular motion after complete division of the mesenteric nerves shows that the movement which occurs during life, like that which takes place *post mortem*, is effected by a mechanism within the intestine; and its continuance in the portion of gut so treated, while other parts were relaxed, on the application of galvanism to the spine, proves that the inhibiting influence acts through the mesenteric nerves, whose integrity is necessary to the effect.

This being established, it follows that if a quiet state of the intestine, such as very frequently occurs in its natural condition, were due to a controlling agency on the part of the so-called "inhibitory system," the complete division of the mesenteric nerves supplying a portion of gut which is at rest, would liberate it from this restraint, and movement would be the result. I performed the operation in one case under such circumstances, but the portion of intestine concerned remained as tranquil as the rest.

To sum up the above, it appears that the intestines possess an intrinsic ganglionic apparatus which is in all cases essential to the peristaltic movements, and, while capable of independent action, is liable to be stimulated or checked by other parts of the nervous system; the inhibiting influence being apparently due to the energetic operation of the same nerve-fibres which, when working more mildly, produce increase of function.

After the above conclusions had been arrived at, my attention was

directed by Professor Goodsir to a paper by Dr. O. Spiegelberg, published last year, in which he shows that the movement of the intestines is increased by mechanical irritation of the cord. His results are particularly satisfactory, as having been obtained incidentally during an inquiry into the movements of the uterus, and so without any preconceived theory*. Spiegelberg also attributes the increased peristaltic action after death to arrest of the circulation; having found that the same thing occurs during life, when the aorta or vena cava is compressed above the origin of the mesenteric vessels.

To proceed to the experiments upon the cardiac movements: some of these consisted in irritation of the vagus in rabbits, and this was followed by different results in different instances: thus, on one occasion the pinching of the cardiac end of the left nerve, divided in the neck, was followed by considerable increase in the number of beats as felt through the walls of the chest, but similar treatment of the right nerve afterwards caused great depression of the heart's action. Again, in one animal the evidence obtained from mechanical irritation of the vagus was almost entirely negative. In another case, the left vagus having been exposed, feeble galvanic currents transmitted through the nerve, isolated by a plate of glass placed beneath it, were succeeded by slight increase in the number of contractions. The strength of the battery having been then increased by introducing the rods into the helix, it produced first irregularity, and then complete arrest of the action of the heart, which had been previously exposed. No sign of recurrence of contraction appearing, I filled the jar to the top with acid solution, and sent powerful currents through the vagus, with the instantaneous effect of reviving the action of the heart, which, on their immediate discontinuance, continued to beat, though feebly, for several minutes. During this time I again applied the galvanism very mildly, and the result was great increase in the number of beats on several successive trials. The apparent discordance of these facts is, I believe, partly owing to differences in the state of the nerves in different cases as respects irritability and exhaustion, as will be better understood from the sequel; and, on the whole, the experiments appear to show that, in a

* Henle and Pfeufer's Zeitschrift, 3rd series, vol. ii. pt. 1.

healthy state of the nervous system, very gentle irritation of the vagus increases the heart's action, while a slightly stronger application diminishes the frequency and force of its contractions. This conclusion is in harmony with an observation which I made incidentally upwards of a year ago, that irritation of the posterior part of the brain of a frog with a fine needle was repeatedly followed by improvement in the circulation, whereas it was by the application of a stronger stimulus, that of galvanism, to the same part of the cerebro-spinal axis that Weber first induced an inhibitory action on the heart.

It is said, on apparently good authority*, that division of the vagus in mammalia is invariably followed by increase of the action of the heart; this, if true, would be a strong ground for believing in an inhibiting influence constantly operating upon it through this nerve. But it is also stated that the same thing does not occur in frogs; and this circumstance appeared to me to throw much doubt upon the evidence regarding mammalia. I therefore made careful experiments on the effects of cutting both vagi, once upon a calf and four times upon rabbits; taking the number of the heart's beats immediately before and immediately after section of each nerve by the momentary stroke of a sharp pair of scissors. In no case was the rate increased at all by the operation, and the very gradual diminution in frequency that commonly took place appeared to depend on general exhaustion from other circumstances attending the experiment. In one rabbit, in which I had removed the skin and pectoralis major from the præcordial region, so as to see the movements of the heart distinctly through the transparent pericardium and intercostal muscles, I noticed particularly that the strength of the contractions, as well as their frequency, remained quite unaffected by the division of the vagi. From these facts I feel warranted in concluding that, whatever may occur under exceptional circumstances, there is certainly no constant control exercised over the heart's action through those nerves.

The influence of the spinal system upon the heart is, however, very apparent after a struggle, which almost invariably increases the frequency and force of the beats; and I found that this continued

* Pflüger, *op. cit.*

to be the case after division of both vagi, implying that those nerves are not the only channels through which this influence is transmitted. A new field of investigation was thus opened. For, supposing the inhibitory agency to be simply the greater action of an ordinary nerve, it would probably not be exercised exclusively by the vagus, but also by the other nerves connecting the cerebro-spinal axis with the cardiac ganglia, viz. the sympathetic branches in the neck; in which case the action of the heart should be increased or diminished, according to the strength of the stimulus, by the application of galvanism to the cervical region of the spine after the pneumogastric nerves had been cut.

In an experiment performed with this view, the poles having been fixed to about the fourth cervical and fifth dorsal spinous processes, and both vagi divided in the neck, galvanic currents only just perceptible to the tip of the tongue were first transmitted. This excessively feeble action of the battery, though apparently not very favourably situated for influencing the cord, produced marked effects upon the heart's action, increasing the number of beats, which were about forty in ten seconds, by from three to ten in that period. This effect having been observed for a considerable time, the rods of soft iron, which had been till then only inserted half-way in the helix, were pushed fully in. The battery, thus strengthened, instead of increasing, as before, the rate of the pulsations, diminished it by two in ten seconds on several successive trials. On again half withdrawing the rods, the galvanism, when applied, again increased the number of beats. A little more of the acid solution was afterwards poured into the jar of the battery, when the stronger currents which it produced reduced the number by about five in ten seconds.

Yet distinct as was this inhibiting influence, the shocks were still quite tolerable to the tongue even when the rods were fully in the helix.

These results were of great interest, as proving how slight an increase of the feeble stimulus which promoted the action of the heart sufficed to produce the opposite (inhibiting) effect. But it was by no means clear that the influence had not been exerted through cardiac branches arising from the vagi above the parts where they were divided, or even through the trunks of those nerves, which might

possibly have been affected by the galvanism acting through the superjacent spinal column. In order to eliminate the vagi completely, I divided in another rabbit all the soft parts in front of the spine, except the trachea and œsophagus, at the level of the cricoid cartilage, having previously cut each carotid artery between two ligatures. The incisions were carried fairly down to the bodies of the vertebræ, and outwards beyond the tips of the transverse processes, so as to ensure the section not only of the vagi and their branches, but also of the sympathetic cords, with any filaments of those nerves which they might contain. Also the poles of the battery were fixed to the spinous processes of the seventh dorsal and first lumbar vertebræ, so as to avoid all possibility of direct action of the galvanism upon either the vagi or other cardiac nerves. Feeble currents being then transmitted, diminution of the number of beats to the extent of two to four in ten seconds occurred in several successive trials, the results being so constant as to leave no doubt that they were produced by the galvanism.

It may appear almost incredible that such extremely mild galvanic currents, applied through the spinous processes of the posterior dorsal region, should be capable of thus affecting the heart; but that their effects were really very considerable, was clear from the further progress of this experiment and from others somewhat similar, which showed that this apparently trivial stimulation gradually exhausted the part of the nervous system through which the heart is acted on by the cord. Thus, in one case, currents only just perceptible to the tongue, transmitted for about thirty seconds at a time through the lower cervical and upper dorsal regions of the spine, at intervals of nine minutes on the average during two hours and twenty minutes, produced at first decided increase of the heart's action, but during the last hour failed to affect it at all. The strongest possible action of the battery which, as proved by other experiments, would, at the outset, have entirely arrested the cardiac movements, was then set on, but with no effect whatever on the organ.

When partial exhaustion has occurred, a much stronger galvanic stimulus is required, to produce the same effect upon the heart, than at the commencement of an experiment; and thus an action of the battery which, when first applied, causes marked diminution in the number of beats, may after a while come to have the opposite effect,

and increase the heart's action as decidedly as it had previously lowered it; while at an intermediate period it may seem to have no influence at all. This principle gives the clue to understanding what had before appeared incomprehensible in these experiments, showing that facts which at first seemed utterly inconsistent, were really perfectly harmonious. The case before related, in which revival of the heart's action resulted from powerful stimulation of the vagus, which, had the organ been contracting as usual, would have arrested its movements and probably finally destroyed them, will now be understood. I have seen other analogous cases of revival of action by very powerful galvanism, which under ordinary circumstances would have arrested it, viz. twice in the heart and twice in the intestines. The observation published so long ago as 1839 by Valentin*, that mechanical or chemical irritation of the vagus in the neck of an animal recently dead, and with the nerves consequently enfeebled, causes contraction of the ventricles, admits of a similar interpretation, as also does a corresponding fact regarding the splanchnic nerves, given without explanation by Kupfer and Ludwig, in a paper just published†, viz. that they lose their inhibitory influence a certain time after death, and acquire a motor power over the intestines.

Two more experiments require mention, as they exclude the possibility of the agency in them, of either the vagi or the part of the brain from which the vagi spring, having been performed upon decapitated rabbits. In one of these cases, the carotids having been tied near the head, the neck was completely severed behind the first vertebra, care being taken to avoid hæmorrhage from the vertebral arteries, and artificial respiration, for which provision had been made, was carried on for an hour and a half after decapitation. The results of moderate galvanism, applied to the posterior dorsal region of the spine, to which the poles had previously been attached, were at first not distinct, but afterwards decided increase of action was produced by it when applied at intervals during half an hour; the effect being perfectly apparent in the heart which lay exposed before me. Exhaustion of the nerves concerned having then taken

* Valentin, De Functionibus Nervorum, p. 62.

† Henle and Pfeufer's Zeitschrift, 3rd series, vol. ii. pt. 3.

place, the most powerful action of the battery failed to influence the character of the contractions.

In the other case, the poles having been fixed as before, and the head similarly removed, powerful galvanic currents were immediately transmitted. The pulsations of the heart in the opened chest at once fell from thirty-five to sixteen in ten seconds, but rose again to twenty on the removal of the stimulus.

Hence it is clear that the sympathetic branches connecting the cord with the cardiac ganglia have equal claims with the vagi to be called "inhibitory nerves." In fact this expression seems to me altogether objectionable, since there is good reason to think that the same fibres which check the movements, much more commonly enhance them. The only evidence afforded by my experiments that the inhibiting influence is ever exerted in the natural actions of the animal, consisted in the quiescence of the intestines sometimes seen after a struggle, and two doubtful observations of retardation of the heart's beats from the same cause. Indeed it appears very questionable whether the motions of either of these viscera are, under ordinary circumstances, ever checked by the spinal system, except for very brief periods; whereas the increased action of both heart and intestines, familiarly known to result from mental emotion, may last for a very considerable time. The fact that the nerves of these organs are capable of setting them at rest under conditions of extraordinary irritation is nevertheless a matter of great importance, especially in a pathological point of view, and appears to afford an explanation of facts in medicine hitherto little understood, —such as failure of the heart's action from violent emotion or pain, and the constipation which attends strangulated omental hernia.

From the observations of Spiegelberg*, it would appear that the uterine contractions are promoted by mechanical irritation of the cord, and arrested by transmitting a powerful stream of galvanism through the spine. Also the forcible expulsion of urine very frequently seen in the lower animals in consequence of fear, and the temporary palsy of the detrusor often witnessed in the human subject in surgical practice as the result of severe injury, seem to me

* Henle and Pfeufer's Zeitschrift, 3rd series, vol. ii. part. 1.

to imply that the bladder, too, while sometimes stimulated through the cerebro-spinal axis, is paralysed by its very powerful operation. Hence it seems probable that the movements of all the hollow viscera are liable to similar influence from the spinal system. At the same time it appears to be a mistake to regard this influence in the light of a strict control; for the experiments related in this letter show pretty distinctly that the contractions of the heart and the peristaltic action of the intestines are regulated, under ordinary circumstances, by the independent operation of the intrinsic ganglia.

Professor Schiff has, I understand, observed increase of the heart's action to result from very gentle stimulation of the vagus*, and has come to the conclusion, as stated by Spiegelberg in his paper before referred to, that the inhibiting influence depends upon nervous exhaustion. There are some circumstances which make me entertain great doubt as to the correctness of this view. In the first place, the very rapid recovery of the cardiac or intestinal actions when the inhibiting galvanic currents are discontinued, contrasts strongly with the length of time that the impairment of function resulting from a protracted experiment, and certainly due to exhaustion, lasts both in the intrinsic cardiac nerves and in those that connect them with the spinal system. Secondly, although very powerful galvanism not only arrests for the time, but permanently impairs the action of the heart, no such effect is observed to follow the inhibiting influence when it is caused by milder stimulation; indeed, according to my experience, less injurious effects are produced upon the heart by a protracted series of experiments of the latter kind than by a corresponding set with the currents still more feeble, that increase, while acting, the frequency of the contractions. But if the diminished rate of the pulsations were caused by a partial exhaustion of the cardiac ganglia, an opposite result might have been anticipated.

Again, there can be little doubt that dilatation of the blood vessels, in consequence of a stimulus, is due to an effect produced upon the nervous centres for the arteries, similar to that experienced by the visceral ganglia when subject to the inhibiting influence. Now an inflammatory blush of long continuance may subside rapidly when

* Henle and Meissner's Bericht, 1857.

the source of irritation is withdrawn. Thus I have seen redness which had existed for about three days in the human skin in consequence of tight stitches connecting the lips of a wound, give place at once to pallor on their removal. Had the arterial dilatation in this case been the result of nervous exhaustion continued during so long a period, such speedy recovery could hardly, one would think, have taken place.

These and other considerations, to which the already excessive length of this letter forbids me to allude, induce me to think it safest in the present state of science to regard as a fundamental truth not yet explained, that one and the same afferent nerve may, according as it is operating mildly or energetically, either exalt or depress the functions of the nervous centre on which it acts. It is, I believe, upon this that all inhibitory influence depends, and I suspect that the principle will be found to admit of a very general application in physiology.

I am, &c.,

JOSEPH LISTER.